Compositions and uses associated with the MT103 family of compounds are disclosed. Particular structural features and properties of the compounds are described in detail. Uses include administering an MT103 family member to a patient for therapeutic purposes. Compositions include chemicals belonging to the MT103 family and pharmaceuticals that contain such chemicals. Methods of treating cells are also described.
FIGURE 3
FIGURE 4
FIGURE 5
Figure 6
THERAPEUTIC AGENTS, METHODS, AND TREATMENTS

CROSS REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] The application is generally related to methods of treating patients with chemical agents, and methods of inhibiting cell growth, including cancer.

BACKGROUND OF THE INVENTION

[0003] Cancer is a disease that afflicts many people and is a leading cause of death in humans and non-human animals. Cancers typically involve cells that grow by uncontrolled growth of the cells that creates many new cells. Many anti-cancer drugs are agents that inhibit or stop cell growth.

[0004] Many anti-cancer drugs are known to be effective against cancers and tumor cells, but some cancers and tumors respond poorly to these drugs. Further, many anti-cancer drugs also destroy other cells in the body. Thus, new anti-cancer drugs are desired, and drugs that are able to target specific cancer types can provide useful therapeutic options.

[0005] Agents that inhibit cell growth are useful as anti-cancer drugs. The National Cancer Institute (NCI) is an agency of the United States government that is involved in the testing of anti-cancer drugs. NCI often conducts initial screening tests of potential anti-cancer drugs using a three cell line test. Each of the three cell lines is a type of cancerous cell. The cells are exposed to the drug candidates, and the drugs’ effectiveness in stopping cell growth and/or killing the cells is measured.

[0006] The NCI typically tests the most promising drugs with a further battery of approximately 60 cell lines, and the dose of the drug that is required to stop cell growth and to kill cells is measured. The dose of the drug that is required to inhibit approximately 50% of the growth of a cancer cell is reported as the GI_{50} concentration of the drug. The lower the GI_{50}, the more effective is the anti-cancer drug. The GI_{50} is sometimes reported in the units of -log (GI_{50}), so that the higher the value for -log (GI_{50}), the more effective is the anti-cancer drug. The dose of the drug that is required to stop approximately 100% of cell growth is reported as the total growth inhibition (TGI) concentration of the drug. The dose of the drug that is required to reduce the number of the cells to 50% of the original number of cells is referred to as the LC_{50} concentration. The lower the TGI or LC_{50}, the more potent is the anti-cancer drug.

SUMMARY OF THE INVENTION

[0007] The invention includes embodiments related to the MT103 family of therapeutic compounds, as shown for example, in Formulas I(a) and I(b), below. An embodiment of the invention is a method of using an MT103 family member for treatment of patients, for example, as a cancer therapeutic, antibacterial, antifungal, apoptosis agent, protein kinase agent, and/or hormonal antagonist. Another embodiment is using a MT103 family member as a therapeutic, antibacterial, antifungal, apoptosis agent, protein kinase agent, and/or hormonal antagonist. Another embodiment is a therapeutic, antibacterial, antifungal, apoptosis agent, protein kinase agent, and/or hormonal antagonist that comprises an MT103 family member, e.g., a chemical according to one of Formulas 1-70 below. Embodiments of the invention include compositions and methods for treating a patient, including providing to, or administering to, a patient a therapeutically effective amount of a composition comprising a chemical as in Formulas 1-70.

[0008] Another embodiment is a chemical according to one of Formulas 1-70 below, or a species thereof. Another embodiment is a pharmaceutical composition associated with a chemical according to one of Formulas 1-70 below, or a species thereof. Another embodiment is a method that includes exposing a cell to a composition comprising a chemical according to one of Formulas 1-70 below, or a species thereof, e.g., for diagnosis, testing, screening, or treatment in vitro or in vivo.

BRIEF DESCRIPTION OF THE FIGURES

[0009] FIG. 1 depicts GI_{50} values for MT103 for a variety of cell lines, with the GI_{50} values being plotted as -log GI_{50}; and


[0011] FIG. 3 is a graph showing inhibition of tumor growth in vivo using a member of the MT103 family, as described in greater detail in Example 7.

[0012] FIG. 4 is a graph of test results showing that a member of the MT103 family to be non-toxic, as described in greater detail in Example 7.

[0013] FIG. 5 is a graph of test results showing a member of the MT103 family was more effective than the anti-cancer drug cisplatin for slowing tumor growth in vivo, as described in greater detail in Example 8.

[0014] FIG. 6 shows dose response curves for MT103 administered at therapeutically suitable amounts, as demonstrated with three lung cancer cell line, as described in greater detail in Example 5.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] An anti-cancer agent referred to herein as MT103 is disclosed (Formula 2), along with derivatives of this molecule that are expected to have an anti-cancer activity. These compounds were developed using computer models that analyze topological features of molecules and help to predict which ones will be effective. The predictive power of these processes have been verified by successful in vitro and in vivo tests of candidate compounds, including those set
forth in the Examples. Variations of the MT103 molecule are described herein that have structural similarity to MT103 that is expected to give them anti-cancer properties.

[0016] The creation of new anti-cancer drugs is a challenging process. An important step is the selection of drug candidates for initial screening. Many approaches for selecting these drug candidates are used. One approach is to use computer modeling to design molecules that have physicochemical properties that are useful as anti-cancer agents.

[0017] Computer Modeling

[0018] A topological computer modeling program that incorporates a molecular shape learning system has been used to identify the new family of drugs exemplified by MT103. The modeling program takes topological information about chemicals that are known to be effective anti-cancer drugs, and in a next step identifies common topological features that the drugs should share to show activity in the property under study. Then the program identifies new chemicals that have the common topological features. The program is designed not only to identify chemicals that are anti-cancer compounds but also to identify chemicals that are useful to combat specific types of cancer. MT103 was identified by the program as a chemical that would inhibit the growth of cancer cells. Further, MT103 was identified as a compound having particular efficacy against non-small lung cancer cells. The fact that a compound was successfully identified with that function is proof of the efficacy and utility of the compounds predicted by the computer model.


[0020] Trained models predict the bioactive topology of molecules and can be readily interpreted to guide the design of new active compounds. This approach combines three advances: a representation that characterizes surface shape such that structurally diverse molecules exhibiting similar surface characteristics are treated as similar; a new machine learning methodology that can accept multiple orientations and conformations of both active and inactive molecules; and an iterative process that applies intermediate models to generate new molecular orientations to produce better predictive models. Two aspects of the program described above, the method of iterative reposing objects to produce better models and the method of training a model when each object has multiple representations, are applicable not only to biological activity modeling but also to other physicochemical characteristics.


[0022] The following examples show that the MT103 family of compounds are effective general anti-cancer agents, and, moreover, that they have selectivity for non-small cell carcinoma cells. The topological computer modeling system described herein was used to generate chemical structures of drugs that are effective against non-small cell carcinoma cells and are active with protein kinase targets, and MT103 was identified as a desirable anti-cancer drug. Subsequent testing by the independent governmental agency NCI provided further evidence that MT103 was an effective anti-cancer drug. Additional experiments with the NCI-H226 cell line provided further proof of the efficacy of MT103. The examples, below, are illustrative and are not intended to be limiting of the invention.

[0023] The term heterocyclic is used herein, meaning a cyclic compound having as a ring member at least two different elements. Cyclic compounds may be aromatic or non-aromatic with at least one ring, e.g., one, two, three, or more rings. An aromatic group can be any conjugated ring system containing 4n+2 π-electrons. There are many criteria available for determining aromaticity. A widely employed criterion for the quantitative assessment of aromaticity is the resonance energy. In some embodiments, the resonance energy of the aromatic group is at least 10 KJ/mol. In further embodiments, the resonance energy of the aromatic group is greater than 0 KJ/mol. Aromatic groups may be classified as an aromatic heterocyclic group which contains at least a heteroatom in the 4n+2 π-electron ring, or as an arene or aryl group which does not contain a heteroatom in the 4n+2 π-electron ring. Nonetheless, either the aromatic heterocyclic or the arene or aryl group may have at least one heteroatom in a substituent attached to the 4n+2 π-electron ring. Furthermore, either the aromatic heterocyclic or the arene or aryl group may comprise a monocyclic or polycyclic (such as bicyclic, tricyclic, etc.) aromatic ring. An arene is a monocyclic or polycyclic aromatic hydrocarbon; an aryl is formed by removal of a hydrocarbon from a ring carbon atom of an arene.

[0024] Non-limiting examples of the aromatic heterocyclic group are furanyl, thiophenyl, pyrrolyl, indolyl, carbazoly, benzofuranyl, benzo[thiophenyl, dibenzofuranyl,
Substitution is liberally allowed on the chemical groups, and on the atoms that occupy a position in a Formula depicted herein, for various physical effects on the properties of the compounds, such as mobility, sensitivity, solubility, compatibility, stability, and the like, as is known generally in the art. In the description of chemical substituents, there are certain practices common to the art that are reflected in the use of language. The term group indicates that the generically recited chemical entity (e.g., alkyl group, alkenyl group, aromatic group, epoxy group, arylamine group, aromatic heterocyclic group, aryalkyl group, aliphatic group, heterocyclic non-aromatic group etc.) may have any substituent thereon which is consistent with the bond structure of that group. For example, where the term ‘alkyl group’ is used, that term would not only include unsubstituted linear, branched and cyclic alkyls, such as methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, dodecyl and the like, but also substituents having heteroatom such as 3-ethoxypropyl, 4-(N-ethylamino)butyl, 3-hydroxypropyl, 2-thiolhexyl, 1,2,3-tribromopropyl, and the like. However, as is consistent with such nomenclature, no substitution would be included within the term that would alter the fundamental bond structure of the underlying group. For example, where a phenyl group is recited, substitution such as 1-amino-phenyl, 2,4-dihydroxyphenyl, 1,3,5-trimethoxyphenyl, 1,3,5-trimethoxyphenyl and the like would be acceptable within the terminology, while substitution of 1,1,2,2,3,3-hexamethylenyl would not be acceptable as such substitution would require the ring bond structure of the phenyl group to be altered to a non-aromatic form because of the substitution. When referring to an epoxy group, the substituent cited includes any substitution that does not destroy the 3-membered ring structure of the epoxy group.

All of these various groups may be optionally derivitized with substituent groups. Suitable substituent groups that may be present on such a “substituted” group include e.g. halogens such as fluor, chloro, bromo and iodo; cyano; H, hydroxyl group; ester group; ether group; a carboxanate, an oxo acid group, an oxocarbon group, an oxo carboxylic acid group, an oxo group, a ketone group; nitro; azido; sulhydryl; alkanoyl e.g. C_{n} alkanoyl group such as acetyl and the like; carboxamido; alkyl groups, alkynyl and alkynyl groups including groups having one or more unsaturated linkages; alkoxy groups having one or more oxygen linkages; aroyloxy such as phenoxy; aroythio groups; alkyrsulfanyl groups; alkylsulfanyl groups; aminoalkyl groups such as groups having one or more N atoms; carbocyclic ary; aroyloxy such as phenoxy; aralkyl having 1 to 3 separate or fused rings; aralkoxy having 1 to 3 separate or fused rings; or a heteroaromatic, heterocyclic, or heteroacylic group having 1 to 4 separate or fused rings e.g., with one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiadiazolyl, oxazolyl, imidazolyl, indolyl, benzofurany1, benzothiazolyl, tetrahydrofuranyl, tetrahydroprpyranyl, piperidinyl, morpholin and pyrrolidinyl. Other substituent groups may include groups that include O, S, Se, N, P, Si, C and have between 2 and about 150 atoms. In some embodiments, it is useful to limit the size of any substituent to, e.g., less than about 150, less than about 100, less than about 50, or less than about 20 atoms.

An alicyclic compound is a cyclic alicyclic compound having at least one ring, e.g., one, two, three, or more rings. The term alicyclic compound refers to an organic compound that is an alkane or alkene or alkylene or their derivative. Examples of alicyclic compounds include cycloalkanes, e.g., cyclobutane, cyclopentane, cyclohexane, cyclooctane, and bicyclo[2.2.1] heptane group. A heterocyclic non-aromatic compound is a compound having at least one ring and at least two different elements in the ring, e.g., an N, O, S or substituted into at least one ring carbon of cyclohexane, cyclooctane, or bicyclo[2.2.1] heptane group.

The term alkyl, unless otherwise specified, refers to a saturated straight, branched, or cyclic hydrocarbon, and specifically includes, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with any appropriate group, including but not limited to one or more groups selected from halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aroyloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art. The term alkenyl, unless otherwise specified, is a straight, branched, or cyclic (in the case of C_{n} alkanes) hydrocarbon with at least one double bond, and may be substituted as described above. The term alkynyl, unless otherwise specified, is a hydrocarbon, straight or branched, with at least one triple bond, and may be substituted as described above. In some embodiments, it is useful to limit the size of these substituents to, e.g., less than about 150, less than about 100, less than about 50, or less than about 20 atoms.
aminonitrenes, nitrenes, aminoxides, nitriles, and nitride imides. Other suitable substituent groups include these and other S-containing compounds, e.g., sulfonic acid, sulfate, sulfonates, sulfamic acids, sulfanes, sulfatides, sulfenamides, sulfenes, sulfenic acids, sulfenium ions, sulfenyl groups, sulfenyl nitrenes, sulfenyl radicals, sulfides, sulfiliumines, sulfilimides, sulfinamides, sulfides, sulfuric acids, sulfinyl anhydrides, sulfinilmines, sulfenylamines, sulfenylphosphines, sulfenylphosphoranes, sulfonamides, sulfonamides, sulfonohydrazines, sulfones, sulfonic acids, sulfonic anhydrides, sulfonamides, sulfonyl compounds, sulfophthaleins, sulfonylamines, sulfoxides, sulfonoxides, sulfonoximes, sulfur diimides, thiois, thioacetals, thioaldehydes, thioaldehyde S-oxides, thiophenylhydrazides, thioarboxylic acids, thiocyanates, thiocetates, thiocarbamates, thioketones, thioacetone S-oxides, thiobutanes, and thionylamines. Other suitable substituent groups include these and other O-containing compounds, e.g., having the form ROH (alcohol), RCOOH (carboxylic acids), RCHO (aldehydes), RR'C=O (ketones), ROR' (ethers), and RCOOR' (esters), with the R denoting a bond or atomic element. Other suitable substituent groups include these and other P-containing compounds, e.g., phosphates, phosphorylidenes, phosphonic acids, phosphazenes, phosphine oxides, phosphines, phosphonic acids, phosphinidens, phosphinous acids, phosphoglycerides, phospholipids, phosphonic acids, phosphonates, phosphorus compounds, phosphonium ylides, phosphono, phosphonous acids, phosphoranes. Carbon is useful for making substituents and the number of carbons in a heteroatomic structure may be, e.g., between 1 and n when between 2 and n atoms are used to form a substituent with, e.g., O, P, S, or N. In some embodiments, it is useful to limit the size of these substituents to, e.g., less than about 150, less than about 100, less than about 50, or less than about 20 atoms.

A variety of substituents are contemplated so that some potential combinations of claimed embodiments may be unstable or impractical to make. A person of ordinary skill in the art can select appropriate stable compounds within the disclosed genus of compounds based on the disclosure herein. Therefore, substituents generally are limited to those substituents that result in appropriate valence for the particular substituted element without forming a charged compound or a radical (except for titratable charged groups, stable zwitterionic forms and triplet neutral radicals with formal unpaired spins with full valences), as can be conventionally determined by a person of ordinary skill in the art.

Introduction to MT103 Family

Formula 1 shows motifs for the MT103 family, and has been found to be significant with respect to therapeutic function by computer modeling.

An embodiment of the invention is a family of drugs, referred to herein as the MT103 family, that is bioactive, affects cellular functions, and inhibits cancer. A species of this family is depicted as Formula 2, referred to herein as MT103, and is known as N,N-dicyclohexyl-18-isoborneol-10-sulfonamide, or N,N-dicyclohexyl-2-hydroxy-7,7-dimethylbicycle[2.2.1]hept-1-ylmethanesulfonamide. Particular stereoisomers/diastereoisomers are set forth herein; persons of ordinary skill in these arts will appreciate that other stereoisomers/diastereoisomers of these structures, and other structures described herein, are also suitable.

A—Z—Y—X

Formula 1(a)

Referring to Formula 1(a), A comprises a bicyclo [2.2.1] heptane group, a heterocyclic group, an aliphatic group, or an aromatic group; Z is a bond or a linking group; Y is a group having one of C, S, O, N, or P; X is —(CH₃)₉—X* group, wherein X* is a H, a halogen, a hydroxyl group, a thiophenyl group, a thiol group, a carbonyl group, an amino group, an alkyl group, an alkane group, an aliphatic group, a heterocyclic group, or an aromatic group; and —(CH₂)n is a group where n is an integer between 1 and about 50, inclusive, and one or more of the methylene groups is optionally replaced by O, S, N, C, B, Si, P, C≡O, O=S=O, a heterocyclic group, an aromatic group, an NR₃ group, a CR₃ group, a CR₄ group, or a SiR₄ where R₁, R₂, R₃, R₄, and R₅ are, each independently, a bond, a pi bond, H, a hydroxyl group, a thiol group, a carbonyl group, a carbamate, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, a sulfonate group, an alkyl group, an alkoxy group, an alkynyl group, an heterocyclic group, an aromatic group, or a part of a ring group. The groups may be substituited as described herein. A person of ordinary skill in these arts can select appropriately stable compounds from the genera of compounds presented or claimed herein based on conventional chemical principles.

Formula 1(b) depicts a subgenus of Formula 1(a), and Formula 1(c) depicts a bicyclo [2.2.1] heptane group.
Referring to Formula 1(b), each line joining two occupied positions is a chemical bond, and a line between an occupied position and a vacant position is a nullity, meaning that it is not necessary to posit each position as having an element or group therein, in which case that position and the bind associated therewith, may be considered to be absent form the formula. the positions in FIG. 1(b) potentially being, but not being limited to:

- A, A', independently comprise C, S, O, or N; A', and A, are, each independently, H, an alkyl group, an alkynyl group, an alkynyl group, or a halogen group except that A, and A, may be combined to form a single group comprising a C or O having a double bond to A,
associated atoms. In all of these formulas, R₆ and R₇ are either a hydrogen or a methyl group. Also, R₈, R₉, R₁₀, R₁ and R₁' are all hydrogen atoms. The R₆', R₉', R₁₀ and R₁₀' are as indicated in the specific formula.

[0046] Alternatively, the alicyclic groups of Formula 3 may have various substituents, as described above, and as exemplified in Formulas 12 and 13.

[0047] Formulas 14 and 15 show additional embodiments of cyclic groups for substitution into Formula 1, e.g., into the R₆ and R₉ positions. Formula 14 depicts a genus of C₅ alicyclic groups, and Formula 15 depicts a genus of C₆ aryl
groups. Potential substituent groups are denoted as having positions $T_1, T_2$, including $T_1', T_2'$. $T$ would be a position in an MT103 structure, e.g., position X in a Formula herein, e.g., Formula 1(a) or 1(b). The chemical groups denoted as $T$ may be, e.g., vacant or a group that is member of the group consisting of a lone electron pair, a bond, a $\pi$ bond, H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether, an ester, a ketone, a carboxyl, a cyclic group, an alicyclic group, an aromatic group, groups that include O, S, Se, N, P, Si, and C and have between 2 and about 150 atoms, or a heterocyclic group. Alternatively, e.g., groups that may depend from cyclic structures in an MT103 family molecule include at least one group independently selected from structures consisting of, e.g., H, OH, O, halogens, alkyl (e.g., $C_1-C_4$), primary amines, secondary amines, tertiary amines, carboxyls, carboxy groups, amides, alkenyl (e.g., $C_1-C_3$), cycloalkanes, cycloaromatics, alyclics, unsaturated rings, aromatic rings, alkenyl (e.g., $C_1-C_3$), alkoxy, and groups of fewer than about 120 atoms having at least one structural element selected from the group consisting O, S, Se, N, P, Si, and C.

As additional examples of cyclic structures, Formula 16 shows a subgenus of compounds with $C_8$ aryls, as in Formula 15, substituted into positions $R_4$ and $R_5$ of Formula 1(b). Formulas 17-25 show various species within the subgenus of Formula 16.
Formula 26 shows an embodiment wherein the $T_2$ and $T_2'$ positions of Formula 16 are bonded to the adjacent ring. In general, $R_a$ and $R_b$ of Formula 1(b), and other formulas herein, may have groups that are connected to each other by a bond or a bridge, e.g., having multiple atoms. The various substitutions and substituents described herein may thus include, for example, groups having bonds to groups in other positions as well as unconnected functional groups, as summarized. For example, the positions denoted as $T$ in Formulas 14, 15, and 16 may be filled with groups that join the cyclic structures to each other.

Another subgenus of Formula 1(a) is directed to groups having at least 4 atoms in positions $R_a$ and $R_b$ of Formula 1(b). Examples of groups for $R_a$ and/or $R_b$ in Formula 1(b) are those groups having $H$, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, an amino group, an amide group, a phosphatate group, an alkyl group, an aryl group, an alkynyl group, an alkoxy group, an oxo group, an ether, an ester, a ketone, a carboxylic group, a cyclic group, an acyclic group, an aromatic group, aromatic groups that include $O$, $S$, $Se$, $N$, $P$, $Si$, $C$ and have between 2 and about 150 atoms, or a heterocyclic group. Formula 27 shows a subgenus having $CH_3$ groups in positions $R_a$ and $R_b$, e.g., with a particular species shown in Formula 28. In other embodiments, the $C_n$ groups may have substituents as described for herein, e.g., for alkyls and alkenyls, as depicted in Formula 29.

Another subgenus of Formula 1(a) and 1(b) has a cyclic group joined by, e.g., an ether bond to occupy at least one of $R_a$-$R_a'$ in Formula 1(b). Formula 30 shows an embodiment of FIG. 1(b) comprising an aryl ring joined with an ether linkage at $R_a$ of Formula 1(b). In Formula 30, $R_a''$-$R_a'''$ may be, e.g., independently chosen to be vacant or a group that is member of the group consisting of a lone pair of electrons, $H$, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, an amino group, an amide group, a phosphatate group, an alkyl group, an aryl group, an alkynyl group, an alkoxy group, an oxo group, an ether, an ester, a ketone, a carboxylic group, a cyclic group, an acyclic group, an aromatic group, aromatic groups that include $O$, $S$, $Se$, $N$, $P$, $Si$, $C$ and have between 2 and about 150 atoms, or a heterocyclic group. The groups and atoms of Formula 30 may be substituted as described herein. Formulas 31-44 show various species within Formula 30, including substituents substituted as described herein.
MT131: N,N-Dicyclohexyl-C-[7,7-dimethyl-2-phenoxo-bicycle[2.2.1]hept-1-yl]-methanesulfonamide

MT103a: N,N-Dicyclohexyl-C-[7,7-dimethyl-2-[2,4,6-trihydroxy-phenoxo]-bicycle[2.2.1]hept-1-yl]-methanesulfonamide

MT103b: N,N-Dicyclohexyl-C-[7,7-dimethyl-2-pentahydroxyphenoxo-bicycle[2.2.1]hept-1-yl]-methanesulfonamide
[0052] Some structures set forth herein as members of the MT103 family lack a bridge structure. Nonetheless, topological aspects of these molecules indicate inclusion in the MT103 family as being suitable, with the structures providing similar topological or structural motifs. For example, Formula 48-54 depict a group of molecules that do not have a bridge.

[0053] Formulas 48 and 49 show examples of subgeneric structures for A in Formula 1(a). These structures may have \( R_1, R_2, R_3, R_4, R_5 \), and \( R_6 \) as described for any of \( R_1 \) in Formula 1(b), and may be substituted as described herein. For example, any of \( R_1, R_2, R_3, R_4, R_5 \), and \( R_6 \) or substituents thereof, may be independently chosen from a lone electron pair, a bond, a pi bond, H, a halogen, a hydroxy group, a thiol group, a sulfonate group, a carboxyl group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an amido group, an ether, an ester, a ketone, a carboxyl, a cyclic group, an aliphatic group, an aromatic group, groups that include O, S, Se, N, P, Si, C, and have between 2 and about 150 atoms, or a heterocyclic group. Formulas 50-54 show species of these subgenera as applied to Formula 1(a) or 1(b).
MT136-8-Hydroxy-1-oxo-3,4-dihydro-1H-isoquinoline-2-sulfonic acid dicyclohexylamide

MT142-8-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid dicyclohexylamide

MT123--N,N-Dicyclohexyl-C-(3-methoxy-phenyl)-methanesulfonamide

[0054] Formula 55, 56 depict subgenera of Formula 1(b) having a N at position X, a S at position Y and an O at position Z; FIG. 56 further depicts a double-bonded O at positions B1 and B2. The other positions may be filled as described with reference to Formula 1(a) or 1(b), and include a choice of leaving one or both positions R3 and R4 as lone electron pairs. Atoms or groups in the positions of these Formulas may be as those described in Formula 1(b), and groups of these Formulas may be liberally substituted, as described herein.

[0055] Formula 57-59 depict a subgenus of Formula 1(b) having a N at position X, a S at position Y, a C at position Z, and a C in positions A1 and A2; Formula 58 further depicts S at position A5, while Formula 59 depicts N at position A6. The other positions may be filled as described with reference to Formula 1(b). Atoms or groups in the positions of these Formulas may be as those described in Formula 1(b), and groups of these Formulas may be liberally substituted, as described herein.
described herein. Formulas 62-65 show certain embodiments of an MT103 family member having a C filling position \( X \) in Formula 1(b).

[0057] Formula 66 and Formula 67 depict subgenera of Formula 1(a) having a S at position \( X \), and a C at position \( Y \); Formula 67 further depicts C at positions \( A_1\)–\( A_8 \). The other positions may be filled as described with reference to Formula 1(b), and include a choice of leaving both positions \( R_6 \) and \( R_7 \) vacant and as lone electron pairs. Atoms or groups in the positions of these Formulas may be as those described in Formula 1(b), and groups of these Formulas may be liberally substituted, as described herein.

[0058] Formulas 68-70 depict a subgenus of Formula 1(b) having cyclic structures in positions \( R_6 \) and \( R_7 \); Formulas 69, 70 further depict N at position \( X \) and S at position \( Y \); Formula 70 further depicts C at positions \( A_1\)–\( A_8 \). The other positions may be filled as described with reference to Formula 1(b). Positions \( T \), including \( T_1\)–\( T_{10} \), \( T_{10}^{'}\)–\( T_{15} \), \( T_{15}^{'}\)–\( T_{15}^{''} \), may be filled as described for any of \( R_1\)–\( R_6 \) in Formula 1(b). Atoms or groups in the positions of these Formulas may be as those described in Formula 1(b), and groups of these Formulas may be liberally substituted, as described herein.
Some chemical groups in MT103 family are believed to be preferable, although other members of the family may have desirable characteristics also. These include hydrogens or short alky1s or alkenyls, particularly methyls, at R₃ and R₄ positions in the Formulas described herein. The C₅ cycloalkyls or their derivatives are considered to be useful at R₅ and R₆. In particular, for R₅ and R₆ such C₅ derivatives that have hydroxyls or carboxyls on at least two positions of the C₅ are useful. The presence of at least one hydroxyl in positions R₅ to R₆ is also believed to be useful, but not essential for function.

MT103, as shown in Formula 1, may be purchased from commercially available sources (e.g., ALDRICH, FLUKA, CAS number 99295-72-4) and may be synthesized as described in *Chiral auxiliary conferring excellent diastereodifferentiation in reactions of O-enoxy and enolate derivatives*, W. Oppolzer, Tetrahedron 43, 1969 (1987) and in W. Oppolzer and *Enantioselective syntheses of-amino acids from 10-sulfonamido-isobornyl esters and di-buty1 azodicarboxylate*, R. Moretti, Tetrahedron 44, 5541 (1988). Oppolzer taught the use of MT103 as an agent useful for making certain kinds of stereospecific compounds. Other researchers have published work that describes MT103, and chemically modified derivatives of MT103, as compounds for stereochemical uses.


Scheme I depicts a synthesis route for making sulfonamides that can be used to make members of the MT103 family. Referring to Scheme I, aryl or alkyl sulfonyl chloride is reacted with a secondary amine in a single-step reaction. If the R, R’, or R” contains reactive groups, e.g., amine or thiol, then protective groups may be used to prevent the production of an excessive number of secondary products. Artisans of ordinary skill will be able to synthesize such variants of MT103 as are set forth herein, and other chemicals that are in the family of chemicals that share the features of MT103. References that address sulfonamide synthesis are, for example: Gong, B.; Zheng, C.; Skrzypeck-Jankun, E.; Yan, Y.; Zhang, J.; J. Am. Chem. Soc. 1998, 120, 11194-11195; Gong, B.; Zheng, C.; Zeng, H.; Zhu, J.; J. Am. Chem. Soc. 1999, 121, 9766-9767; Neckolls C., Hof, F.; Martin, T.; Rebek J Jr.; J. Am. Chem. Soc. 1999, 121, 10281-10285; R. Ohme; H. Preuschhol. Liebigs Ann. Chem. 713, 74-86 (1968); Tetrahedron Letters, 38, 50, 8691-86 (1997); and Bernmann, Manfred, Van Wazer, John R. Synthesis (1972), (10), 576-7.

Scheme II presents a general scheme for synthesis of carboxamides. An amine having R and R’ may be reacted with an acyl chloride to form a structure as depicted in Scheme II. If R or R’ contains, e.g., amine, carboxylic, or hydroxyl groups, then protective groups may be used to prevent the production of an excessive number of secondary products. The protective groups for amine, carboxylic, and hydroxyl groups are described in Carey, Advanced Organic Chemistry, 2nd Ed., Part B, page 539-552 (1983).

Schemes III(a) and III(b) show the synthesis of members of the MT103 family that contain bicyclic bridges, with MT136, in Formula 50 being used as an example in Scheme III(a). In these scheme, a group, e.g., a bicyclic bridge comprising an amide (Scheme III(a)) or a secondary amine (Scheme III(b)) is derivatized to sulfamoyl chloride by reacting the amide or amine with sulfonyl chloride. The sulfamoyl chloride is reacted with a secondary amine in a single-step reaction. The OCH₃ group is converted to OH in the last step. With respect to reaction of butyl lithium (BuLi) in tetrahydrofuran (THF), the reaction temperature is preferably at about -78° C.
Scheme III(a)  Synthesis of MT136

```
\[ \text{BnLi} \quad \text{THF} \quad \text{SO}_2\text{Cl}_2 \]
```

[0066] Scheme IV presents a scheme for adding methyl groups to an MT103 family structure, with MT147, in Formula 5, and a variant thereof being used as examples. TBS is t-butyl-dimethyl silyl, LDA is lithium diisopropylamide, Mel is methyl iodide, TBAF is tetrabutyl ammonium fluoride.

```
1) LDA/THF
2) Mel
```
[0067] Persons of ordinary skill in these arts can accomplish the synthesis of the precursors needed for making the embodiments of the invention according to Schemes I-IV outlined above, as well as other suitable reactions. Many of the precursors for reaction in the various schemes herein are available commercially and can be readily used or modified, e.g.:

- Diphenylamine
  - CAS Number 122-39-4

- Phenoxazine
  - CAS No. 135-67-1

- 5H-Dibenz[b,f]azepine
  - CAS No. 256-96-2

- 3-amino-4-phenylamino-benzoic acid

- (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonyl chloride
  - CAS 1939-99-7

- 6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-Pyrimidine-5-sulfonyl chloride
  - CAS 1939-99-7
Other embodiments within the MT103 family have the Y group being an oxygen atom. Suitable reactions, for example, involve the formation of an ether linkage —C—O—C—. Persons of ordinary skill in the art recognize that ether linkages can be formed from a sulfuric acid catalyzed de-hydrolysis reaction of two corresponding alcohols or from a reaction between a halide substituted compounds with an alkoxide. In further embodiments, the Y group of the compound is a carbon atom, which can form, for example, a —C—C— linkage. Carbon-carbon bonds can be formed using a Grignard reagent, in which a compound R—C—MgBr reacts with a compound Br—C—R" to form R—C—C—R". Some embodiments are directed to the use of phosphorus in the MT103 family. Various other reaction schemes can be followed by a person of ordinary skill in the art to form the various stable compounds within the MT103 family based on the representative teachings herein.

Phosphorus is multivalent and can form bonds with varying number of atoms (Coordination Number), which can vary from 1 to 6. Phosphorus can form bonds with many other elements and can be substituted into Formulas and reaction schemes as appropriate to satisfy its valency requirements. It has empty d-orbitals which readily accept electrons from donors. In many circumstances, phosphorus can extend its number of bonds to take a new group and via a substitution reaction more readily than carbon. Phosphorus can form bonds readily with oxygen, nitrogen and sulfur, and also can form bonds with carbon. These four bonds enable the linkage of phosphorus to organic compounds to make organophosphorus compounds. References for phosphorus chemistry include, e.g., A Guide to Organophosphorus Chemistry, Louis D. Quin, January 2000 (ISBN: 0-471-31824-8); Organophosphorus Chemistry—A Practical Approach in Chemistry, Edited by Patrick J. Murphy, University of Wales, Bangor, June 2004. Various other reaction schemes can be followed by a person of ordinary skill in the art to form the various stable compounds within the MT103 family based on these and other representative teachings herein.

MT103 Family Compounds

The compounds described herein are designed for activity against non-small cell lung cancer, which is a type of lung neoplasm. To provide some perspective, 95% of primary lung neoplasms are bronchogenic carcinoma/epithelial neoplasms. Bronchogenic carcinoma is commonly divided into two groups: small cell lung cancer, which accounts for about 20% of all cases; and non-small cell lung cancer, which accounts for about 80% of all cases. The non-small cell lung cancer group is further divided into 3 tumor categories based on cell morphology. One category is Squamous cell carcinoma (also called epidermoid carcinoma), which accounts for about 40% of non-small cell lung cancer cases. The second category is Adenocarcinoma, which accounts for 45% of all cases and is the most common lung cancer in non-smokers. The remaining 10% of cases are Large cell lung cancers, which are rapidly fatal.

As shown in Examples 2-5, MT103 has demonstrated in vitro activity against all three categories of non-small cell lung cancer, as demonstrated by tests with multiple cells, including HOP-92 cells (Large cell model), NCI-H460 (Large cell model), NCI-H522 (Adenocarcinoma model), and NCI-H226 cell line (Squamous cell model). As demonstrated by further tests, MT103 is effective against cancer cells in general and is particularly effective against non-small lung cancer cells. In fact, MT103 has a \( \log \text{IC}_{50} \) value of 5.6, see FIG. 1 as tested by the NCI in the HOP-92 non-small lung cancer cell line, a large value that indicates that MT103 is particularly effective against this type of cancer, see Table 3. Additional tests conducted by another independent source confirmed this activity, and showed that MT103 has a \( \log \text{IC}_{50} \) value of 4.6 for HOP-92, see Table 5 in Example 5. This same series of tests showed that MT103 has a \( \log \text{IC}_{50} \) value of 5.1 against the NCI-H226 and 4.1 against NCI-H522, see Table 5 in Example 5. The members of the MT103 family that share motifs of MT103 are therefore also expected to have the anti-cancer function of MT103, as well as its mode of action, and other functions.

Computer modeling and comparison to other chemicals shows that MT103 and the MT103 family are anti-cancer agents, inducers of apoptosis agents, protein kinase agents, hormonal antagonists, antibacterials, antifungals, and hypolipidemics. Examples 1 and 6 show the results of computer models that predict efficacy for the MT103 family. As shown in Examples 1 and 6, chemicals used for such comparisons are paclitaxel, topotecan, etoposide, tamoxifen, anastrozole, and flutamide. Examples 2-5 and 7-8 show that the computer models were successful for predicting the in vitro and in vivo effectiveness of MT103.
The NOD/SCID induced-tumor mouse model used in Example 7 is a useful predictor of efficacy in human subjects. It showed that MT013 was effective in vivo and was safe. In this model, MT013 slowed down H226 tumor progression, see FIG. 3, and did not cause detectable toxic side effects, see FIG. 4.

Further tests with this model, using the NCI-H226 squamous carcinoma cell line, as shown in Example 8, showed that MT013 was comparable to, or superior to, the anti-cancer drug cisplatin, see FIG. 5. A range of doses were tested, with 120 mg/kg showing the most improvement compared to cisplatin. Examples 7 and 8 show that MT013 was well tolerated in the animal model and was statistically significantly equivalent to, or better than, cisplatin at all doses tested.

Since the MT013 family of drugs generally have desirable characteristics, e.g., as outlined in Examples 1 and 6, and as shown by computer modeling and comparisons, they may be used to treat patients to inhibit cancer and to act in the patients as apoptosis agents, protein kinase agents (e.g., PKC-alpha inhibition), hormonal antagonists, antibacterial agents, antifungals, and hypolipidemic. Cells in vitro and in vivo may be exposed to members of the MT013 family for this purpose. MT013 and the MT013 family can be useful not only as drugs for treating or curing certain cancer types but also as drugs that inhibit certain cancer types in humans and non-human animals. Further, apoptotic agents, hormonal antagonists, antibacterial agents, and antifungals are important commercial products that are used in many ways; similarly, members of the MT013 family may also be used for such purposes. Accordingly, potential uses would include use for diagnostics, cell testing, and as chemical reagents for commercial sale.

Hypolipidemic drug therapy is used in cases of hyperlipidemia (hypercholesterolemia) to reduce cholesterol levels. These drugs have been used in well-controlled studies of patients with high cholesterol levels caused primarily by elevated levels of low-density lipoproteins (LDL). The results of these trials indicate that coronary heart disease (CHD) mortality is reduced by as much as 30% to 40% and that nonfatal events are similarly reduced when hypercholesterolemic patients are treated with moderate doses of hypolipidemic drugs [Scandinavian Simvastatin Survival Study Group, 1994; Shepard et al., 1995; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998].

Further, the MT013 family of chemicals may be used in vitro or in vivo to slow or stop cell growth, kill cells, or to inhibit the growth of cells in vitro or in vivo. Apoptosis inducers, protein kinase agents, and hormonal antagonists are valuable research tools for in vitro and in vivo treatment of cells. Antibacterials and antifungals are valuable products for suppressing, inhibiting and/or killing bacteria and fungi in vitro, in vivo, ex vivo, and in a multitude of environments such as residential, commercial, hospital, and industrial settings. These compounds may be used alone or in combination with other drugs to achieve the most suitable therapy for a patient or other purposes. Appropriate patients include any animals that can benefit from such therapy and include mammals, such as humans, farm animals and pet animals.

Anti-cancer compounds that are effective against one type of cancer can be expected to have an anti-cancer effect against other types of cancers. As shown in Example 3, e.g., Table 3, MT013 displays activity against a wide variety of cancer types. While some compounds described herein may be clinically preferable for use in certain types of cancer, they are also expected to be useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, hairy cell lymphoma and Burkitt’s lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi’s sarcoma. According to another embodiment of the invention, compounds of the invention are directed to therapies for cell proliferative disorders, for example, Alzheimer’s disease, viral infections, auto-immune diseases and neurodegenerative disorders.

MT013 and the MT013 family are also useful when delivered in combination with medical devices. For example, the devices may be implantable for a short period of time, or an extended time. Other medical devices are only transiently introduced into the body. Examples of implants made for an extended period of time are stents, e.g., use in blood vessels or other portions of the body, heart valves, pacemakers, defibrillators, angioplasty devices, artificial blood vessels, artificial hearts, and indwelling catheters. Examples of devices implantable for short periods of time include temporary catheters, oxygenator lines, blood pumps, blood filters, and drug delivery systems. Examples of devices introduced only transiently are guidewires, balloons for e.g., angioplasty, and rapidly degradable devices. Other medical devices used with a member of the MT013 family may be devices deployed temporarily, permanently, or semi-permanently in contact with blood, e.g., sensors, biosensors, and diagnostic kits.

One use of MT013 family compounds is to inhibit cell growth around an implanted device. The inhibition may be for a short time, for example while the body’s inflammatory reaction is most active, or on a longer term basis. For example, an MT013 family member may be delivered using a strategy of sustained release, slow release, e.g., by enteric coating. The inhibition of cell growth is a significant strategy for the prevention of restenosis after angioplasty or implanting a stent in a blood vessel. Inhibition of cell growth is also a significant strategy for enhancing the biocompatibility of implanted devices so that the reaction of the body to the devices is minimized.

Cells may be exposed to a member of the MT013 family. Exposure can be useful for, e.g., therapeutic treatments, for testing, for diagnosis, and research. The activities
of MT103 are useful for studying certain aspects of cellular metabolism and function, e.g., cell growth, or models of disease states such as cancer. Cells is a term used broadly, and includes cells in vitro, in vivo, prokaryotic, eukaryotic, and fungal.

Administration of Compositions

Pharmaceutically acceptable salts of the compounds described herein may be synthesized according to methods known to those skilled in this art, see, for example, Pharmaceutical Salts: Properties, Selection, and Use, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor) June 2002. Generally, such salts are prepared by reacting the free base forms of these compounds with a stoichiometric amount of the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of some appropriate salts are found, for example, in Remington’s Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985.

In some embodiments, the compounds described herein are used in combination with one or more modulators and/or chemotherapeutic agents for the treatment of cancer or tumors. Examples and descriptions of potentiation and combination therapies are provided in, for example, U.S. Pat. Nos. 6,200,929 and 6,352,844.

The compounds described herein may be administered as a single active drug or a mixture thereof with other anti-cancer compounds, and other cancer or tumor growth inhibiting compounds. The compounds may be administered in oral dosage forms that include tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Further, the compounds may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form.

The compounds described herein are typically to be administered in admixture with suitable pharmaceutical diluents, excipients, extenders, or carriers (termed herein as a pharmaceutically acceptable carrier, or a carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The deliverable compound will be in a form suitable for oral, rectal, topical, intravenous injection or parenteral administration. Carriers include solids or liquids, and the type of carrier is chosen based on the type of administration being used.

Techniques and compositions for making dosage forms useful for materials and methods described herein are described, for example, in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington’s Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7, (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.)

Suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents may be included as carriers, e.g., for pills. For instance, an active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like.

Suitable binders include, for example, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, for example, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds may also be used with liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds may also be coupled to polymers as targetable drug carriers or as a produrg. Suitable biodegradable polymers useful in achieving controlled release of a drug include, for example, polyactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, caprolactones, polyhydroxy butyric acid, polyorthoesters, polyacetics, polydihydroxyprans, polysycaocylates, and hydrogels, preferably covalently crosslinked hydrogels.

The active compounds can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. The active compounds can also be administered parenterally, in sterile liquid dosage forms.

Capsules may contain the active compound and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similarly, such diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for continuous or long-term release of the active compounds. The deliverable form of the compounds can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

For oral administration as a liquid, the drug components may be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples liquid forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solu-
O
tions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring, as needed. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington’s Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The compounds described herein may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches known to those skilled in these arts. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

The compounds set forth herein may also be used in pharmaceutical kits for the treatment of cancer, or other purposes, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of the compound. Such kits may further include, if desired, one or more of various components, such as, for example, containers with the compound, containers with one or more pharmaceutically acceptable carriers, additional containers, and instructions. The instructions may be in printed or electronic form provided, for example, as inserts or labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

Dosage levels include from about 0.1 mg to about 2000 mg of active compound per kilogram of body weight per day are preferable dosages; persons of ordinary skill in these arts will recognize that all doses and ranges between these explicit values are contemplated, e.g., 0.1 to 100, and 1 to 50 mg/kg. The amount of active compound that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 0.1 mg to about 10,000 mg of an active compound; persons of ordinary skill in these arts will recognize that all doses and ranges between these explicit values are contemplated. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. For example, a suitable dosage adopted for oral or intravenous administration of a compound of the MT103 family may range from about 0.1 to about 1000 mg per dose, from 1 to 5 times daily.

The method of administration of the compounds set forth herein can be any suitable method that is effective in the treatment of the particular cancer or tumor type being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into a tumor or cancer. The method of applying an effective amount also varies depending on the disorder or disease being treated. Parenteral treatment may be, e.g., by intravenous, subcutaneous, or intramuscular application of the compounds set forth herein, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application.

The MT103 compound is commercially available and has been described as useful for certain sterosechemical reactions, as referenced in the Synthesis section, herein. Some members of the MT103 family, however, have not been previously disclosed by others. Further, the MT103 family is described herein as having anticancer uses, and as having other biological activities. Embodiments of the invention include compositions that contain a compound as set forth herein, e.g., as in Formulas 1-70.

EXAMPLES

Example 1

N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide predicted to be an effective anti-cancer agent by topological computer modeling.

Table 1 shows the output for the topological computer model for selected anti-cancer agents and for N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide. This output indicates that N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide is an effective anti-cancer agent. As a control for the computer model, the computer model was also used to predict the results for known anti-cancer agents such as paclitaxel and topotecan, as well as for ifosfamide and Busulfan, agents that are typically not employed as anticancer agents. As indicated in Table 1, N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide is predicted to be effective for multiple types of cancer, with a -logGI50 value of at least 6.3 for each type of cancer that was tested.

<table>
<thead>
<tr>
<th>Activity against breast cancer</th>
<th>MT103</th>
<th>Paclitaxel</th>
<th>Topotecan</th>
<th>Ifosfamide</th>
<th>Busulfan</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-MCF7</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>1-log(GI50), molar</td>
<td>7.2</td>
<td>8.8</td>
<td>7.5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

TABLE 1

Topological computer model results for MT103 and selected anti-cancer compounds.
### TABLE 1-continued

<table>
<thead>
<tr>
<th>Modeled Properties for Compounds</th>
<th>MT103</th>
<th>Paclitaxel</th>
<th>Epotinα</th>
<th>Ifofarnide</th>
<th>Busulfan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity against lung cancer</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>NCI-H460 -log(G_{50}) molar</td>
<td>6.3</td>
<td>7.4</td>
<td>7.6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Activity against CNS cancer</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>NCI-SF268 -log(G_{50}) molar</td>
<td>7.3</td>
<td>7.6</td>
<td>7.0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Protein Kinase C Inhibitor, Log K_{i}, mM</td>
<td>0.9</td>
<td>0.1</td>
<td>2</td>
<td>&gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Induction of Apoptosis</td>
<td>21%</td>
<td>69%</td>
<td>3.6%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

[0104] The pharmacokinetic properties of MT103 have been calculated and result in some predictions that show the usefulness of the chemical. The predictions indicate that MT103 will decay according to a 2 or 3 compartment model with a predicted terminal elimination half-life of about 3 hours. An average peak plasma concentration of about 1 mg/L should occur about an hour after dosing. The total clearance is estimated to be about 25 L/h and the mean apparent volume of distribution at steady state as about 1.5 L/kg. The expected mean oral bioavailability of MT103 is about 20% and about 79% of the MT103 in the plasma is bound to protein in the body. Analogs having a structure similar to MT103 are expected to have similar pharmacokinetic properties.

**Example 2**

[0105] NCI three-cell line test indicates that N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide is an effective anti-cancer agent.

[0106] This Example shows that MT103 is predicted by in vitro cell testing to be an effective anti-cancer agent. The testing in this Example was performed by NCI, as per their 3-cell line panel test. The results are reported as the percent of the growth of the treated cells compared to the untreated control cells. The criterion for being an effective compound and for being subjected to further testing is that the tested compound reduce the growth of any one of the three cell lines to approximately 32% or less. As shown in Table 2, MT103 was much more effective than the commonly accepted scientific accepted criterion; in fact, MT103 reduced the growth of all three cell lines to 16% or less at the one concentration tested.

### TABLE 2

<table>
<thead>
<tr>
<th>MT103 shown to be effective by NCI 3 cell-line test.</th>
<th>Growth, Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of MT103 in growth medium</td>
<td>MCF7 Cell Line (Breast Cancer)</td>
</tr>
<tr>
<td>(10^{-4}) Molar</td>
<td>16</td>
</tr>
</tbody>
</table>

[0107] The methods for conducting the test are described below in Example 3, except that the cells were exposed to a single concentration of MT103, at 1x10^{-4} Molar, and colorimetric determinations were made with alamar blue (Biotechniques 21(5):780-782 (1996)).

**Example 3**

[0108] NCI sixty cell line test shows that MT103 is an effective anti-cancer drug.

[0109] The NCI tested MT103 with 60 cell lines, and reported the G_{150}, T_{GI}, and L_{C50} values of MT103 for each cell line, see FIG. 1 and Table 3.

### TABLE 3

<table>
<thead>
<tr>
<th>NCI 60 cell-line test for the drug MT103.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel/Cell Line</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>CCRF-CEM</td>
</tr>
<tr>
<td>HL-60 (TB)</td>
</tr>
<tr>
<td>K-562</td>
</tr>
<tr>
<td>MDA-MB-231</td>
</tr>
<tr>
<td>RPMI-8226</td>
</tr>
<tr>
<td>SR</td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td>A549/ATCC</td>
</tr>
<tr>
<td>EKVX</td>
</tr>
<tr>
<td>HOP-62</td>
</tr>
<tr>
<td>HOP-92</td>
</tr>
<tr>
<td>NCI-H23</td>
</tr>
<tr>
<td>NCI-H22M</td>
</tr>
<tr>
<td>NCE-H460</td>
</tr>
<tr>
<td>NCI-H22</td>
</tr>
<tr>
<td>Colon Cancer</td>
</tr>
<tr>
<td>COLO 205</td>
</tr>
<tr>
<td>CTC-16</td>
</tr>
<tr>
<td>HCT-11</td>
</tr>
<tr>
<td>HCT-116</td>
</tr>
<tr>
<td>HCT-15</td>
</tr>
<tr>
<td>HCT-116</td>
</tr>
<tr>
<td>MDA-MB-231</td>
</tr>
<tr>
<td>SW-620</td>
</tr>
<tr>
<td>Metastasis</td>
</tr>
<tr>
<td>SF-268</td>
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<tr>
<td>SF-295</td>
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<tr>
<td>SF-539</td>
</tr>
<tr>
<td>SNB-19</td>
</tr>
<tr>
<td>SNB-75</td>
</tr>
<tr>
<td>U251</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
<tr>
<td>LOX IMVI</td>
</tr>
<tr>
<td>MALME-3M</td>
</tr>
<tr>
<td>M14</td>
</tr>
<tr>
<td>SK-MEL-2</td>
</tr>
<tr>
<td>SK-MEL-28</td>
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TABLE 3-continued

<table>
<thead>
<tr>
<th>NCI 60 cell-line test for the drug MT103</th>
<th>Panel/Cell Line</th>
<th>G150</th>
<th>TGI</th>
<th>LC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK-MEL-5</td>
<td>1.68E-05</td>
<td>3.61E-05</td>
<td>7.77E-05</td>
<td></td>
</tr>
<tr>
<td>UACC-257</td>
<td>2.85E-05</td>
<td>9.53E-05</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>UACC-62</td>
<td>1.88E-05</td>
<td>4.65E-05</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGROV1</td>
<td>3.48E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
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</tr>
<tr>
<td>OVCAR-3</td>
<td>2.30E-05</td>
<td>6.30E-05</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>OVCAR-4</td>
<td>3.02E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
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</tr>
<tr>
<td>OVCAR-5</td>
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<td>5.70E-05</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>OVCAR-8</td>
<td>2.95E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>SK-OV-3</td>
<td>8.32E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
<td></td>
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<tr>
<td>Renal Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>786-0</td>
<td>4.63E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
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<tr>
<td>A498</td>
<td>3.04E-05</td>
<td>9.07E-05</td>
<td>1.00E-04</td>
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<tr>
<td>ACHN</td>
<td>2.38E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
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<tr>
<td>Caki-1</td>
<td>2.35E-05</td>
<td>9.05E-05</td>
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<tr>
<td>RXF 593</td>
<td>2.42E-05</td>
<td>9.77E-05</td>
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<tr>
<td>SNU182</td>
<td>3.30E-05</td>
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</tr>
<tr>
<td>TK-10</td>
<td>2.16E-05</td>
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</tr>
<tr>
<td>UO-31</td>
<td>2.80E-05</td>
<td>8.94E-05</td>
<td>1.00E-04</td>
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</tr>
<tr>
<td>Prostate Cancer</td>
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<td></td>
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<td></td>
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<tr>
<td>PC-3</td>
<td>2.78E-05</td>
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</tr>
<tr>
<td>DU-145</td>
<td>3.05E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
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<tr>
<td>Breast Cancer</td>
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<td></td>
<td></td>
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<tr>
<td>MCF7</td>
<td>2.08E-05</td>
<td>9.05E-05</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>NCEABR-RES</td>
<td>3.49E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>MDA-MB-231/ATCC</td>
<td>1.69E-05</td>
<td>4.71E-05</td>
<td>1.00E-04</td>
<td></td>
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<tr>
<td>HS 578T</td>
<td>2.93E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
<td></td>
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<tr>
<td>MDA-MB-435</td>
<td>2.84E-05</td>
<td>9.88E-05</td>
<td>1.00E-04</td>
<td></td>
</tr>
<tr>
<td>MDA/SC</td>
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<td>1.00E-04</td>
<td>1.00E-04</td>
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<tr>
<td>BT-540</td>
<td>5.93E-05</td>
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<tr>
<td>T-47D</td>
<td>6.20E-05</td>
<td>1.00E-04</td>
<td>1.00E-04</td>
<td></td>
</tr>
</tbody>
</table>

[0110] Methodology: The NCI conducted a test of the MT103 drug against 60 human cell lines, with a minimum of five concentrations of MT103 at 10-fold dilutions. A 48 hour continuous drug exposure was used, and a sulforhodamine B (SRB) protein assay was used to estimate cell viability and growth. The human tumor cell lines of the cancer screening panel were grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. Cells were inoculated into 96 well microtiter plates in 100 μL at plating densities ranging from 5,000 to 40,000 cells/7C well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37°C, 5% CO2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs.

[0111] After 24 h, two plates of each cell line were fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). MT103 was solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate was thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions were made to provide a total of five drug concentrations plus control. Aliquots of 100 μL of these different drug dilutions were added to the appropriate microtiter wells already containing 100 μL of medium, resulting in the required final drug concentrations.

[0112] Following drug addition, the plates were incubated for an additional 48 h at 37°C, 5% CO2, 95% air, and 100% relative humidity. For adherent cells, the assay was terminated by the addition of cold TCA. Cells were fixed in situ by the gentle addition of 50 μL of cold 50% (v/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4°C. The supernatant was discarded, and the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 μL) at 0.4% (w/v) in 1% acetic acid was added to each well, and plates were incubated for 10 minutes at room temperature. After staining, unbound dye was removed by washing five times with 1% acetic acid and the plates were air-dried. Bound stain was subsequently solubilized with 10 mM trizma base, and the absorbance was read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology was the same except that the assay was terminated by fixing settled cells at the bottom of the wells by gently adding 50 μL of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements (time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)), the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

\[
\frac{[(Tz)-C]}{(Tz)}\times100\text{ for concentrations for which } Tiz<Tz
\]

\[
\frac{[(Tz)-T]}{(Tz)}\times100\text{ for concentrations for which } Tiz<Tz.
\]

[0113] Three dose response parameters were calculated for each experimental agent. Growth inhibition of 50% (GI50) was calculated from [(Tz)-C]/(Tz)×100=50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) was calculated from Tiz/Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from [(Tz)-T]/(Tz)×100=50. Values were calculated for each of these three parameters if the level of activity is reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

Example 4

[0114] N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide is an effective inhibitor of the cell growth of the cancerous cell line NCI-H226.

[0115] This Example shows that MT103 is a drug for treating human cancer, particularly non-small cell lung cancer. MT103 was tested with the NCI-H226 human non-small cell lung cancer cell line, and effectively inhibited growth of the cancer, see FIG. 2. The GI50 for MT103 was 66 μM.

[0116] Methods The MTS assay was employed in the evaluation of these compounds. The cells were harvested, centrifuged to remove the medium, and suspended in fresh complete medium. Samples were taken to determine cell
density. The cell count was determined with a Coulter Model Z cell counter and viability was measured with propidium iodine staining call by analysis on Coulter EPICS flow cytometer. The cell line was plated at 5x10^5 cells per well in complete medium. On the following day, the cells were closed with the dilutions of the compound. The plates were analyzed on Day for after initiation of treatment.

[0117] The cell line was propagated using standard tissue culture procedures and seeded in microtiter plates prior to dosing. Control groups included a mock treatment, media control, and a positive control (doxorubicin, 1 μM). For each concentration level, eight replicates were treated. The cell line was propagated under sterile conditions at 37° C in 5% CO₂ and 95% humidity. MT103 was stored at 4° C until dissolved and diluted in complete medium.

[0118] Anti-cellular effects of the compound were assessed with the MTS dye conversion assay. MTS was purchased as a single solution, and stored at −20° C. Sample wells were treated with 20 microliters of the MTS solution and the plates were incubated for four hours at 37° C. to allow for conversion into the liquid soluble formazan product. The absorbance of formazan in each monolayer was measured at 490 nm on a Coulter microplate reader at four hours after addition of the MTS.

Example 5

Dosage levels for human use.

These results show the activity of MT103 at dose levels suitable for human use and assess anticellular activity. Testing was conducted employing standard tissue culture techniques and an anchorage-independent colony-forming assay.

MT103 was tested against the lung carcinoma cell lines NCI-H226, NCI-H522, and HOP-92. An anchorage-independent colony-forming assay was employed. For the experiment, the cells were harvested, centrifuged to remove the media, and suspended in Iscove’s Modified Dulbecco’s Medium (IMDM). Samples were taken to determine cell density. The cell count was determined with a Coulter Model Z cell counter and viability was measured with propidium iodide staining followed by analysis on a Coulter EPICS XL flow cytometer. Each cell line was plated at 1x10^5 cells per dish (35 mm) in IMDM with 20% FBS and 1% methylcellulose containing the appropriate concentration of test compound or DMSO control. Five concentrations of each compound and a DMSO control were tested in each of the three cell lines. The colonies per plate were counted on Day 14 after the initiation of treatment. The cell lines were propagated under sterile conditions and incubated at 37° C. in HEPA-filtered CO₂ tissue culture incubators with 5% CO₂ and 95% humidity. The cell line was subcultured weekly to b-weekly and used in experiments. The test compounds were kept refrigerated under light protected conditions until dissolved in DMSO.

Anticellular effects of the compounds on the tumor line were assessed with a colony-forming assay. Briefly, the cell were harvested and adjusted to 3x10^6 viable cells/mL in IMDM. Compounds (200x) were prepared in DMSO and serially diluted in DMSO to give appropriate testing concentrations. Cells (100 μL), compound or DMSO control (16.5 μL) and IMDM (183.5 μL) were added to the appropriate assay tubes (12x75 mm) containing 3 mL of complete media, IMDM with 20% FBS and 1% methylcellulose. Tubes were then vortexed and 1.1 mL of the cell suspension was added to each of two 35 mm dishes. These dishes were then incubated for 14 days in HEPA-filtered CO₂ tissue culture incubators with 5% CO₂ and 95% humidity. The colonies in each dish were then counted and the duplicates were averaged and reported.

Table 5

<table>
<thead>
<tr>
<th>Compound</th>
<th>NCI-H226</th>
<th>NCI-H522</th>
<th>HOP-92</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT103</td>
<td>0.8</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>36.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>65.6</td>
<td>0</td>
<td>43.3</td>
</tr>
<tr>
<td>100</td>
<td>92.2</td>
<td>57.2</td>
<td>100</td>
</tr>
<tr>
<td>500</td>
<td>99.7</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Example 6

Analogs of MT103 determined to be effective therapeutic agents.

Results of the topological computer model showed that members of the MT103 family are effective therapeutic agents. Table 6 shows compounds tested with the computer model and determined to be efficacious. MT103 is N,N-dicyclohexyl-(1S)-isoborneol-10-sulfonamide. Analog B is N-cyclohexyl-N-(3,4-dimethycyclohexyl)-2,3-dihydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide. Analog C is N1-cyclohexyl-N1-{4-[(E)ethylidene]-3-methylenecyclohexyl}-1-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)-1-ethylenesulfonamide. Analog D is 4-cyclohexyloxy][1-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl]vinyl]sulfanamido-2-methyl-1,3 cyclohexanedicarboxylic acid. Analog E is 4{3,4-dihydroxyethylcyclohexyl}(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]sulfanamido]-2-methyl-1,3-cyclohexanedicarboxylic acid.
TABLE 6

Species of MT103 family tested by computer modeling and determined to be efficacious

<table>
<thead>
<tr>
<th>Compound</th>
<th>MT103</th>
<th>Analog A</th>
<th>Analog B</th>
<th>Analog C</th>
<th>Analog D</th>
<th>Analog E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl cholinesterase inhibitor</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
<td>&gt;90%*</td>
</tr>
<tr>
<td>Peak time (hours)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Peak concentration (ng/L)</td>
<td>1</td>
<td>0.04</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Metabolites (% of hepatic elimination)</td>
<td>26</td>
<td>8</td>
<td>59</td>
<td>95</td>
<td>74</td>
<td>40</td>
</tr>
<tr>
<td>Activity against breast cancer (log[OH], molar)</td>
<td>&gt;90%* (7.2)</td>
<td>&gt;90%* (7.0)</td>
<td>&gt;90%* (7.3)</td>
<td>&gt;90%* (7.3)</td>
<td>&gt;90%* (7.4)</td>
<td>&gt;90%* (7.6)</td>
</tr>
<tr>
<td>Activity against lung cancer (log[OH], molar)</td>
<td>&gt;90%* (6.3)</td>
<td>&gt;90%* (6.3)</td>
<td>&gt;90%* (6.4)</td>
<td>&gt;90%* (6.6)</td>
<td>&gt;90%* (6.6)</td>
<td>&gt;90%* (6.8)</td>
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<tr>
<td>Activity against CNS cancer (log[OH], molar)</td>
<td>&gt;90%* (7.3)</td>
<td>&gt;90%* (7.0)</td>
<td>&gt;90%* (7.4)</td>
<td>&gt;90%* (7.4)</td>
<td>&gt;90%* (7.5)</td>
<td>&gt;90%* (7.5)</td>
</tr>
<tr>
<td>Induction of apoptosis (%)</td>
<td>21</td>
<td>25</td>
<td>40</td>
<td>40</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Log Ki (nM) for inhibitors of Protein Kinase-C</td>
<td>0.9</td>
<td>1.5</td>
<td>0.8</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*These percentages indicate calculated probabilities that the compound will have the indicated function.

Example 7

[0127] In vivo test data showing safety

[0128] This experiment provides in vivo test data showing that the MT103 family of compounds is safe and well tolerated, as measured by weight control of the test subjects, and were effective anti-cancer agents over the duration of the test. MT103 slowed down H226 tumor progression significantly in NOD/SCID mice, (NOD.CB17-Prkdcscid/J) without any evidence of toxicity. The change that occurred with the treatment is greater than would be expected by chance (p=0.03).  

[0129] A standard induced-tumor NOD/SCID mouse model was used to perform this investigation, with the mouse model being based on protocols for human xenograft systems developed at the National Cancer Institute. H226 cell cancer tumors were induced in NOD/SCID mice; tumors at sizes approximately 100 mm³ were treated with 30 mg/kg MT103 or a control containing only vehicle (2.5% DMSO in distilled water) administered in intraperitoneal injections every other day for two weeks. As shown in FIG. 4, MT103 did not have deleterious effect on mice body weight. FIG. 3 shows that tumor volume was significantly decreased.

Example 8

[0130] In vivo test data showing efficacy.

[0131] This experiment provides in vivo test data showing that the MT103 family of compounds are effective anti-cancer agents. Comparison to the anti-cancer drug cisplatin showed that MT103 had a comparable or superior effect, depending upon the dosages administered. MT103 was tested at three dose levels (60, 120, and 240 mg/kg). Experiments were performed as described in Example 7, NOD/SCID mice, (NOD.CB17-Prkdcscid/J) except that tumors were treated with: one of three doses of MT103 or Cisplatin or sham for 3 intraperitoneal injections (one every 4 days) in a 2-cycle 56-day test that was extended to another cycle to 86 days, as reflected in FIG. 5. Tumor volumes were measured every other day. As shown in FIG. 5, mean tumor growth slowed in mice receiving MT103, which demonstrated significant efficacy (p=0.046). There were no observable differences in organ appearance in control versus animals treated with 120 mg/kg MT103. Also, there were no differences in blood counts and electrolytes between these two groups.

[0132] In another experiment, NOD/SCID mice, (NOD.CB17-Prkdcscid/J) were treated over a time course with 60 mg/kg of MT103 or a sham treatment, and a different lung cancer cell line was used, A549 (an adenocarcinoma), instead of NCI-H226 (a squamous carcinoma). In this second experiment, there was a delayed onset of tumor growth in the treated group, but the subsequent growth curve had a similar slope compared to the control group. Nonetheless, tumors in the treated group were significantly smaller than the control groups (i.e. 30 days).

[0133] The examples set forth herein are exemplary and are not intended to limit the scope or spirit of the invention. Many embodiments of the MT103 family have been set forth herein; persons of ordinary skill in these arts will appreciate, after reading this disclosure, additional variations and alternatives that may be accomplished; such variations and alternative would therefore fall within the scope of this disclosure. Patents, patent applications, journal articles, and publications that have been referenced in this application are hereby incorporated by reference herein.
What is claimed is:

1. A method for treating a patient, the method comprising administering to the patient a therapeutically effective amount of a composition comprising a chemical comprising the formula \( A \to Z \to Y \to X \), wherein

\( A \) is a bicyclo[2.2.1]heptane group, a heterocyclic group, an aliphatic group, or an aromatic group;

\( Z \) is a bond or a linking group;

\( Y \) is a group having one of \( C, S, O, N, \) or \( P \);

\( X \) is \(-\text{(CH}_2\text{)}_n\) or \(-X^*\) group, wherein

\( X^* \) is a \( H \), a halogen, a hydroxyl group, a thiol group, a carboxyl group, an amino group, an alkyl group, an alkoxy group, an alkynyl group, an alkenyl group, a heterocyclic group, or an aromatic group; and

\(-\text{(CH}_2\text{)}_n\) is a group where \( n \) is an integer between 1 and about 50, inclusive, and one or more of the methylene groups is optionally replaced by \( O, S, N, C, B, Si, P, C=O, O=S=O, \) a heterocyclic group, an aromatic group, an NR group, a CR group, a CR\(_2\) group, or a SiR\(_2\) group, where \( R, R, R, R, R, \) and \( R, \) are each independently, a bond, a \( \pi \) bond, \( H \), a hydroxyl group, a thiol group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, a sulfonate group, an alkyl group, an alkoxy group, an alkynyl group, an alkenyl group, an aromatic group, or a ring group.

2. The method of claim 1, wherein \( Y \) is one of

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{C} \\
\text{P} \\
\text{O} \\
\end{array}
\]

3. The method of claim 1, wherein \( Y \) comprises at least one substituent that is \( H \), alkyl group, alkenyl group, alkynyl group, hydroxyl group, or halogen.

4. The method of claim 1, wherein \( Z \) is a \(-\text{(CH}_2\text{)}_n\) group, wherein \( n \) is an integer between 1 and 10, inclusive, and one or more of the methylene groups is optionally replaced by \( O, S, N, C, B, Si, P, C=O, O=S=O, \) a heterocyclic group, an aromatic group, an NR group, a CR group, a CR\(_2\) group, or a SiR\(_2\) group, where \( R, R, R, R, R, \) and \( R, \) are each independently, a bond, \( H \), a hydroxyl group, a thiol group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkyne group, an alkynyl group, an alkenyl group, an alcohol group, an ether group, an ester group, a ketone group, a carboxyl group, a carbamate group, an aliphatic group, a cyclic group, an aromatic group, a heterocyclic group, or a ring group.

5. The method of claim 1, wherein at least one of \( A, X, \) \( Y, \) and \( Z \), further comprises at least one substituent group chosen to be a halogen, \( H \), hydroxyl group, ester group, ether group, an oxo acid group, an oxocarbon group, an oxo carboxylic acid group, an oxo group, an alkene group, a ketone group, an aldehyde group, a sulfhydryl group, an alkanoyl group, a carbamoyl group, an alkyl group, an alkyl group, an alkyne group, an alkyne group, an alkene group, an alkyne group, an alkyne group, a cyclic group, a heterocyclic group, or a ring group.

6. The method of claim 1, wherein \( A \) has the formula \( A \to A_\text{\(A\)} \), with at least one substituent group chosen from \( R, R_\text{\(A\)} \), and \( R, R_\text{\(A\)} \); \( Z \) has at least one substituent group chosen from \( R, R_\text{\(A\)} \); \( Y \) has at least one substituent group chosen from \( B, B_\text{\(A\)} \), and \( X \) has at least one substituent group chosen from \( R, R_\text{\(A\)}, R, R_\text{\(A\)} \), so that the chemical formula is

\[
\begin{array}{c}
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\text{A} \\
\end{array}
\]

wherin

\( A_\text{\(A\)} \), \( A_\text{\(A\)} \), and \( A_\text{\(A\)} \) independently comprise \( C, S, O, \) or \( N \);

\( A_\text{\(A\)} \) and \( A_\text{\(A\)} \) are, each independently, \( H \), an alkyl group, an alkenyl group, an alkynyl group, an aliphatic group, an aromatic group, a heterocyclic group, or a cyclic group comprising a \( C \) or \( O \) having a double bond to \( A_\text{\(A\)} \);

\( R_\text{\(A\)} \), \( B_\text{\(A\)} \), \( C_\text{\(A\)} \), \( D_\text{\(A\)} \), \( E_\text{\(A\)} \), \( F_\text{\(A\)} \), and \( G_\text{\(A\)} \) are independently chosen to be a lone electron pair, a \( \pi \) bond, \( H \), a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxo carbon group, an amide group, an alkyl group, an alkene group, an alkyl group, an alkene group, an alkyl group, an alkene group, an aromatic group, or a heterocyclic group; and

\( R_\text{\(A\)} \) and \( R_\text{\(A\)} \) comprise at least four atoms.
7. The method of claim 6, wherein at least one of \( R_a \) and \( R_o \) comprises a cyclic group.

8. The method of claim 7, wherein the cyclic group is a heterocyclic group.

9. The method of claim 8 wherein the heterocyclic group comprises a ring having at least one member of the group consisting of S, N, O and P.

10. The method of claim 7, wherein the cyclic group is alicyclic.

11. The method of claim 7, wherein the cyclic group is aromatic.

12. The method of claim 7 wherein the cyclic group further comprises a substituent group that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphorus group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

13. The method of claim 6 wherein at least one of \( B_1 \) and \( B_2 \) comprises O.

14. The method of claim 6 wherein at least one of \( R_a \), \( B_1 \), \( B_2 \), \( R_1 \)-\( R_5 \), \( R_1 \)-\( R_5 \), \( R_6 \), and \( R_7 \) comprises a substituent that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

15. The method of claim 14 wherein at least one of \( A_1 \)-\( A_3 \) has a substituent that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

16. The method of claim 6 wherein \( A_1 \)-\( A_3 \) are C, X is N, Y is S, Z is C, \( R_o \) is a lone electron pair or a bond, \( B_1 \) and \( B_2 \) are each O with a double bond to the Y.

17. The method of claim 16 wherein the chemical comprises a formula chosen from the group consisting of

-continued

![](image)
18. The method of claim 6, wherein $\Lambda_{1}-\Lambda_{2}$ are $C_{4}$, $A_{8}$ and $A_{9}$ each comprise a methyl group, $Z$ is $C$, $Y$ is $S$, $B_{1}$ and $B_{2}$ are each $O$ with a double bond to the $Y$, $X$ is $N$, and $R_{8}$ and $R_{9}$ each comprise a $C_{6}$ alicyclic group so that the chemical formula is:

![Chemical Structure](image)

wherein

$R_{1}-R_{7}$ and $R_{1}'-R_{7}'$, are independently chosen to be a lone electron pair, a pi bond, $H$, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

19. The method of claim 18 wherein at least one of the cyclic groups depicted in the formula of claim 16 further comprises a substituent that comprises $H$, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

20. The method of claim 6, wherein $\Lambda_{1}-\Lambda_{2}$ are $C_{4}$, $A_{8}$ and $A_{9}$ each comprise a methyl group, $Z$ is $C$, $Y$ is $S$, $B_{1}$ and $B_{2}$ are each $O$ with a double bond to the $Y$, $X$ is $N$, and $R_{8}$ and $R_{9}$ each comprise a $C_{6}$ aromatic group so that the chemical formula is:

![Chemical Structure](image)

wherein

$R_{1}-R_{7}$, $R_{1}'-R_{7}'$, $T_{1}-T_{7}$, and $T_{1}'-T_{7}'$ are independently chosen to be a lone electron pair, a pi bond, $H$, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

21. The method of claim 20 wherein the chemical comprises a formula chosen from the
22. The method of claim 6, wherein A₁-A₇ are C; A₈ and A₉ each comprise a methyl group, Z is C; Y is S, B₁ is O, B₂ is O, X is N, and R₀ and R₁ each comprise a methyl group so that the chemical formula is:

```
\[ R_{1}-R_{2}-R_{3}-N-\text{V} \]
```

wherein R₁-R₇ and R₁'-R₇' are independently chosen to be a lone electron pair, a pi bond, H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

23. The method of claim 22 wherein at least one of the methyl groups substituent to the N depicted in the formula of claim 22 has at least one substituent independently chosen to be an alkyl group, an alkenyl group, a halogen group, a cyclic group, a heterocyclic group, an aromatic group, or a heterocyclic group.

24. The method of claim 22 wherein the chemical comprises a formula chosen from the group consisting of

```
\[ R_{2}-R_{3}-N-\text{V} \]
```

wherein R₂-R₇ and R₂'-R₇' are independently chosen to be a lone electron pair, a pi bond, H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

25. The method of claim 6, wherein A₁-A₇ are C; A₈ and A₉ each comprise a methyl group, Z is C; Y is S, B₁ is O, B₂ is O, X is N, R₀ and R₁ each comprise an alicyclic group, and the chemical formula is:

```
\[ R_{1}-R_{2}-R_{3}-N-\text{V} \]
```

wherein R₁-R₇ and R₁'-R₇' are independently chosen to be a lone electron pair, a pi bond, H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

26. The method of claim 25, wherein at least one of the cyclic groups depicted in the formula of claim 16 further comprises a substituent that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

27. The method of claim 25 wherein the chemical comprises a formula chosen from the group consisting of
28. The method of claim 4, wherein A has the formula \( \text{A}-\text{A} \), with at least one substituent chosen from \( \text{R}_1-\text{R}_2 \), and \( \text{R}_3-\text{R}_4 \); \( Z \) comprises \( Z_1 \) and \( Z_2 \) and has at least one substituent chosen from \( \text{R}_5, \text{R}_6, \text{R}_7 \), and \( \text{R}_8 \); \( Y \) has at least one substituent chosen from \( \text{B} \) and \( \text{B}' \), and \( X \) has at least one substituent chosen from \( \text{R}_9, \text{R}_10, \) and \( \text{R}_11 \), so that the chemical formula is

![Chemical Structure](image)

wherein

\( \text{A}_1-\text{A}_2 \) independently comprise \( \text{C}, \text{S}, \text{O}, \) or \( \text{N} \);

\( \text{A}_3 \) and \( \text{A}_4 \) are, each independently, \( \text{H} \), an alkyl group, an alkynyl group, or a halogen group except that \( \text{A}_3 \) and \( \text{A}_4 \) may be combined to form a single group comprising a \( \text{C} \) or \( \text{O} \) having a double bond to \( \text{A}_2 \);

\( \text{R}_5, \text{R}_6, \text{R}_7, \text{R}_8, \text{R}_9, \text{R}_10, \text{R}_11, \text{R}_12, \) and \( \text{R}_13 \) are independently chosen to be a lone electron pair, a pi bond, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, an alkyl group, an alkynyl group, an alkenyl group, an alkylene group, an alkoxy group, an o xo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group;

\( \text{R}_14, \text{R}_15, \) and \( \text{R}_16 \) comprise at least four atoms.

29. The method of claim 28, wherein at least one of \( \text{R}_1 \) and \( \text{R}_2 \) comprises a cyclic group, a heterocyclic group, a heterocyclic group comprising a ring having at least one member of the group consisting of \( \text{S}, \text{N}, \text{O}, \) and \( \text{P} \); an alicyclic group, and an aromatic group.

30. The method of claim 29 wherein the cyclic group further comprises a substituent group that comprises \( \text{H} \), a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkenyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

31. The method of claim 29 wherein at least one of \( \text{A}_1-\text{A}_2 \) has a substituent that comprises \( \text{H} \), a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkenyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

32. The method of claim 1 wherein \( \text{A} \) comprises a heterocyclic group comprising formula

![Chemical Structure](image)

wherein

\( \text{R}_1, \text{R}_1', \text{R}_2, \text{R}_2', \text{R}_3, \text{R}_3', \) and \( \text{R}_4' \) are independently chosen to be a lone electron pair, a pi bond, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkenyl group, an alkylene group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

33. The method of claim 32 wherein at least one of \( \text{R}_5 \) and \( \text{R}_6 \) comprises a cyclic group, a heterocyclic group, a heterocyclic group comprising a ring having at least one member of the group consisting of \( \text{S}, \text{N}, \text{O}, \) and \( \text{P} \); an alicyclic group, and an aromatic group.

34. The method of claim 32 wherein the formula of claim 30 further comprises a substituent group that comprises \( \text{H} \), a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkenyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

35. The method of claim 32 wherein at least one of \( \text{R}_5, \text{R}_6, \text{R}_7, \text{R}_8, \) and \( \text{R}_9' \) has a substituent that comprises \( \text{H} \), a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkynyl group, an alkenyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

36. The method of claim 32 wherein the chemical comprises a formula chosen from the group consisting of

![Chemical Structure](image)
37. The method of claim 4, wherein A has the formula \( A_1 - A_2 \) with at least one substituent chosen from \( R_1 - R_6 \), and \( R_1' - R_6' \); \( Z \) comprises at least one substituent chosen from \( R_9 \), \( R_9' \), and \( R_9'' \); \( Y \) comprises at least one substituent chosen from \( B_1 \) and \( B_2 \), and \( X \) is C, and comprises at least one substituent chosen from \( R_8 \) and \( R_8'' \), so that the chemical formula is

\[
\begin{align*}
\text{wherein} \\
A_1 - A_2 & \text{ independently comprise C, S, O, or N;} \\
A_9 \text{ and } A_9' & \text{ are, each independently, H, an alkyl group, an alkyl group, or a halogen group except that } A_9 \text{ and } A_9' \text{ may be combined to form a single group comprising a C or O having a double bond to } A_2; \\
R_9', B_1, B_2, R_1 - R_6, & \text{ R}_1' - R_6', R_9, \text{ R}_9', \text{ and } R_9'' \text{ are independently chosen to be a pi bond, a lone electron pair, H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxo-}
\end{align*}
\]

carbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group; and

\( R_8 \) and \( R_8'' \) comprise at least four atoms.

38. The method of claim 37, wherein at least one of \( R_8 \) and \( R_8'' \) comprises a cyclic group, a heterocyclic group, a heterocyclic group comprising a ring having at least one member of the group consisting of S, N, O and P, an alicyclic group, or an aromatic group.

39. The method of claim 37 wherein the cyclic group further comprises a substituent group that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

40. The method of claim 37 wherein at least one of \( A_1 - A_2 \) has a substituent that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

41. The method of claim 37 wherein the chemical comprises a formula chosen from the group consisting of

42. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent associated with a therapeutically effective amount of a chemical comprising a formula of \( A-Z-Y-X \), wherein

A is a bicyclo [2.2.1] heptane group, a heterocyclic group, an alicyclic group, or an aromatic group.
Z is a bond or a linking group;
Y is a group having one of C, S, O, N, or P;
X is \(-\text{(CH}_2\text{)}_n\) \(-\text{X}^*\) group, wherein

\(-\text{X}^*\) is a H, a halogen, a hydroxyl group, a thiol group, a carboxyl group, an amine group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group, a heterocyclic group, or an aromatic group; and

\(-\text{(CH}_2\text{)}_n\) is a group where \(n\) is an integer between 1 and about 50, inclusive, and one or more of the methylene groups is optionally replaced by O, S, N, C, B, Si, P, C\(=\text{O}\), O\(=\text{S}\)=O, a heterocyclic group, an aromatic group, a CR group, a CR group, a CR group, or a SiR\(_2\)R\(_3\) where R\(_1\), R\(_2\), R\(_3\), and R\(_4\) are, each independently, a bond, a pi bond, H, a hydroxyl group, a thiol group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amide group, a phosphine group, a sulfonate group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group, a heterocyclic group, an aromatic group, or a part of a ring group.

43. The composition of claim 42, wherein the chemical is a salt.

44. The composition of claim 42, wherein the carrier or diluent comprises at least one member of the group consisting of binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents.

45. The composition of claim 42, wherein at least one of A, X, Y, and Z further comprises at least one substituent group chosen to be a halogen, H, a hydroxyl group; ester group; ether group; an oxo group, an oxocarbon group, an oxo carboxylic acid group, an oxo group, a ketone group; nitro group; azido group; sulfhydryl group; alkenyl group, a carboxamide group; an alkyl group, an alkene group; an alkenyl group, an alkyloxy group; a carboxyl group, an amine group, an amide group; an aryl group, an aryloxy group; an arylthio group; an arylsulfanyl group; and an arylsulfonyle group; an aminoalkyl group; an aralkoxy group; a heteroaromatic group, a heterocyclic group, a heterocyclic group, an amine group, an amide group; an imidion amino group; a nitrogen oxide group, an amine oxide group; an aliphatic group, an aromatic group; an aromatic group; an aromatic group; a heterocyclic group; and

R\(_4\), an R\(_5\), comprise at least four atoms.

47. The composition of claim 46, wherein at least one of R\(_4\) and R\(_5\) comprises a cyclic group.

48. The composition of claim 47, wherein the cyclic group is a heterocyclic group.

49. The composition of claim 47, wherein the heterocyclic group comprises a ring having at least one member of the group consisting of S, N, O and P.

50. The composition of claim 47, wherein the cyclic group is aliphatic.

51. The composition of claim 47, wherein the cyclic group is aromatic.

52. The composition of claim 47 wherein the cyclic group further comprises a substituent group that comprises H, a halogen, a hydroxyl group, a thiocarbonyl group, a carboxyl group, an amide group, a phosphorus group, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, an aromatic group, or a heterocyclic group.
53. The composition of claim 46 wherein at least one of B₁ and B₂ comprises O.

54. The composition of claim 46 wherein at least one of Rₙ, B₁, B₂, R₁, R₂, R₃, R₄, R₅, and R₆ comprises a substituent that comprises H, a halogen, a hydroxyl group, a thiol group, a sulfonate group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an oxo group, an ether group, an ester group, a ketone group, a cyclic group, an alicyclic group, an aromatic group, or a heterocyclic group.

55. The composition of claim 46 wherein at least one of A₁-A₂ are C, X is N, Y is S, Z is C, R₃⁻ is a lone electron pair or a bond, B₁ and B₂ are each O with a double bond to the Y.

57. A method of affecting a cell, the method comprising exposing a cell to a chemical comprising

a formula of A—Z—Y—X, wherein

A is a bicyclic [2.2.1] heptane group, a heterocyclic group, an alicyclic group, or an aromatic group;

Z is a bond or a linking group;

Y is a group having one of C, S, O, N, or P;

X is —(CH₂)ₙ—X*, wherein

X* is a H, a halogen, a hydroxyl group, a thiol group, a carboxyl group, an amino group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group, a heterocyclic group, or an aromatic group; and

—(CH₂)ₙ is a group where n is an integer between 1 and about 50, inclusive, and one or more of the methylene groups is optionally replaced by O, S, N, C, B, Si, P, O==O, O==S==O, a heterocyclic group, an aromatic group, an NRₜ group, a CRₜ group, a CRₙRₜ group, or a SiRₘRₖ where Rₘ, Rₖ, Rₜ, Rₜ, Rₖ, and Rₘ are each independently a bond, a π bond, H, a hydroxyl group, a thiol group, a carboxyl group, a carbamate group, an oxocarbon group, an amino group, an amido group, an amide group, a phosphate group, a sulfonate group, an alkyl group, an alkoxy group, an alkyl group, an alkynyl group, an amino group, or a part of a ring group.

58. The method of claim 57, wherein the chemical is a salt.

59. The method of claim 57, wherein at least one of A, X, Y, and Z further comprises at least one substituent group chosen to be a halogen, H, hydroxyl group; ester group; ether group; an oxo acid group, an oxocarbon group, an oxo carboxylic acid group, an oxo group, a ketone group; nitro group; azido group; sulfhydryl group; alkanoyl group, a carboxamido group; an alkyl group, an alkenyl group, an alkyne group, an alkoxy group, an aryloxy group; an alkylthio group; an alkylsulfanyl group; an alkylsulfonyl group; an aminoalkyl group; an aralkoxy group, a heteroaromatic group, a heterocyclic group, a heterocyclic group, an amine group, an amide group, an amidium ion group, an amine imide group, an amine oxide group, an amonium ion group, an aminonitrene group, a nitrene group, an aminooxide group, a nitrile group, a nitrile imide group, a sulfonic acid group, a sulfite group, a sulfonate group, a sulfamic acid group, a sulfane group, a sulfatide group, a sulfenamide group, a sulfene group, a sulfenic acids group, a selenium ion group, a sulfenyl group, a selenylimium ion group, a sulfenyl nitrene group, a sulfenyl radical group, a sulfide group, a sulfolimine group, a sulfimide group, a sulfimine group, a sulfinamide group, a sulfinimine group, a sulfine group, a sulfonic acid group, a sulfinic acid group, a sulfonic anhydride group, a sulfonamide group, a sulfonylimine group, a sulfonamide group, a sulfonic acids group, a sulfonic anhydride group, a sulfonamide group, a sulfonium group, a sulfonphthalein group, a sulfamidylamine group, a sulfoxide group, a sulfoximide group, a sulfoximine group, a sulfur diimide group, a thiol group, a thioacetic group, a thioaldehyde group, a thioaldehyde S-oxide group, a thiophenyl group, a thiocarbonylic acid group, a thiocyanate group, a thioether group, a thiocarbamates group, a thioether group, a thiocarbamate group, a thionylamine group, an alcohol group, a carboxylic group, an aldehydes group, a ketone group, an ether group, an ester group, a phosphane group, a phosphonylenide group, a phosphatic acid group, a phosphazenes group, a phosphine oxide group, a phosphine group, a phosphinic acid group, a phosphinidenes group, a phosphine oxide group, a phosphoglycerides group, a phospholipid group, a phosphonic acid group, a phosphonitrites group, a phosphonium group, a phosphonium ylide group, a phosphoronic group, a phosphorus acid group, a phosphoramides group, or a phosphorane group.